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Outcomes of deprescribing interventions in older patients with life-limiting illness and limited life expectancy: A systematic review

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Aims: Older patients with life-limiting illness (LLI) and limited life expectancy (LLE) continue to receive potentially inappropriate medicines, consequently deprescribing is often necessary. However, deprescribing in this population can be complex and challenging. Therefore, we aimed to investigate the evidence for outcomes of deprescribing interventions in older patients with LLI and LLE.

Methods: Studies on deprescribing intervention and their outcomes in age ≥65 years with LLI and LLE were searched using PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature, PsycINFO and Google Scholar. Medication appropriateness was primary outcome, while clinical and cost-related outcomes were secondary. Eligibility, data extraction and quality assessment were followed by a narrative synthesis of data.

Results: Of 9 studies (1375 participants), 3 reported on primary outcome. One study showed a significant reduction in medication inappropriateness by 34.9% ($P < .001$) from admission to close-out, the second achieved 29.4% ($P < .001$) and 15.1% ($P = .003$) reduction at 12 and 24 months, respectively. The third reported that their intervention stopped (17.2%) and altered the dose (2.6%) of high-risk medications. Commonly reported clinical outcomes were mortality ($n = 3$), quality of life ($n = 2$) and falls ($n = 2$). Outcomes in terms of cost were reported as overall cost ($n = 2$), medication cost ($n = 1$) and health care expenditure ($n = 1$).

Conclusion: Our findings suggest that deprescribing in older patients with LLI and LLE can improve medication appropriateness, and has potential for enhancement of several clinical outcomes and cost savings, but the evidence needs to be better established.

KEYWORDS

deprescribing, terminally ill, end-of-life, older adults, outcomes, systematic review

1 | INTRODUCTION

The older population with life-limiting illness (LLI) and/or limited life expectancy (LLE) frequently face the burden of potentially inappropriate medication (PIM)[1-4] and polypharmacy,[1,2,5-9] which are known to be associated with poor health outcomes such as reduced quality of life (QOL), adverse drug reactions, falls, hospitalisation and mortality.[9-16] It has been suggested that diagnosis of LLI or LLE should favour discontinuation of preventive medicines.[17-19] However, evidence in the literature indicates that older patients continue to

Principal investigator statement: There is no principal investigator for this study.

receive preventive medicines, or medicines that are not prescribed as symptomatic treatment, without consideration of the diagnosis of LLI.[20,21] Statins, antiplatelets, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, anti-osteoporosis medications, calcium channel blockers, antidiabetics, antiulcer medications, vitamins, and mineral supplements are frequently prescribed to patients with LLI, and they continue to receive them despite being arguably inappropriate.[20,21]

Deprescribing as an intervention is achieved by carefully tapering and withdrawing medications using appropriate tools or algorithms, and possibly through consensus of a multidisciplinary team often led by a physician or pharmacist.[20] However, deprescribing in older patients with LLI under palliative care is complex for several reasons. Firstly, the amplified complexity of physiological changes in this population such as body mass, metabolism and elimination, along with the possibility of cachexia, can potentially alter the pharmacokinetics and pharmacodynamics of any medication being used.[22,23] Secondly, there is a paucity of evidence on deprescribing guidelines in this group of patients. Thirdly, it has been reported that clinical studies tend to exclude around 80% of individuals due to medical comorbidities that include LLIs, and almost 40% of participants are excluded due to being aged >65 years.[24] Lastly, a review on deprescribing trials states that there are limited studies exploring the clinical outcomes of deprescribing in those <65 years and the results are inconsistent.[25] Therefore, taking into consideration all these factors, together with the high prevalence of polypharmacy and PIM, deprescribing interventions in older people with LLI and under palliative care is imperative yet challenging.

Systematic reviews on deprescribing of PIMs or discontinuation of preventive medication in patients with LLI and reduced life expectancy have been conducted.[17,20,21] The findings from these reviews illustrate that older patients with LLI and LLE continue to receive preventive medication. Deprescribing of preventive medication upon the diagnosis of LLE has been encouraged, but the lack of availability of appropriate guidelines complicates the process.[17] There was also wide variation in the assessment of inappropriateness of preventive medication in LLI[20] and opinions of experts on medication optimisation at the end-of-life (EOL).[21] However, these studies did not report the impact of deprescribing interventions on medication appropriateness, clinical outcomes and cost. Therefore, the aim of this systematic review is to investigate the evidence of the outcomes of available deprescribing intervention in older patients with LLI and LLE.

What is already known about this subject

- Medication inappropriateness is associated with poor health outcomes but older patients with life-limiting illness and limited life expectancy continue to receive them.
- Deprescribing of inappropriate medications in these patients is complex and challenging.
- Evidence on the impact of deprescribing intervention on medication appropriateness, clinical benefits and cost-saving is limited.

What this study adds

- Deprescribing interventions can improve medication appropriateness in older people with life-limiting illness and limited life expectancy.
- The impact of deprescribing on clinical outcomes and cost is currently unclear.
- A clinically useful plan for deprescribing medicines that are used for both prevention and symptom control is necessary.

2 | METHODS

2.1 | Protocol and registration

The protocol of this systematic review was registered in PROSPERO (CRD42019119331)[26] and was conducted in adherence with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.2 | Definitions

- *Deprescribing intervention:* Tapering or withdrawal or stopping of an inappropriate medication, supervised by a health care professional, with the goal of reducing or managing polypharmacy and improving patient outcomes through the use of explicit and implicit criteria.
- *Preventive medicines:* Any medicine used for prevention of disease such as lipid lowering agents, antihypertensive agents, antidiabetic medications, antiplatelet medications, bisphosphonates.
- *LLI:* Terminal illness that limits the life expectancy such as advanced or end-stage condition of cancer, dementia, heart failure, chronic obstructive pulmonary disease, and kidney disease.
- *LLE:* Life expectancy of up to 2 years in those with LLI in advanced state or end stage or those under palliative care or those at the EOL or those terminally ill or frail.
- *PIMs:* Medicine(s) or medication class(es) that should generally be avoided in ≥65 years either due to their ineffectiveness or unnecessarily high risk for older person or when a safe alternative is available for similar disease condition.
- *Potentially inappropriate prescription (PIP):* Prescription of any medicine that is considered as PIM.
- *Medication Appropriateness Index (MAI):* A common implicit approach to measure potentially inappropriate prescribing in older adults, using a set of 10 questions with the highest score of 18 for maximum inappropriateness.

2.3 | PICO

- *Population:* Older adults aged >65 years with LLI and LLE up to 2 years, considering advanced state of LLI, terminal illness, EOL situation, palliative state and frailty if LLE not stated or not clearly defined.
- *Intervention:* Deprescribing.
- *Comparison:* Usual care or any head-to-head intervention.
- *Outcome:* Medication appropriateness, clinical measures and costs.

2.4 | Inclusion and exclusion criteria

All types of controlled studies (randomised controlled trials [RCTs] and non-randomised controlled trials) involving older patients having mean age ≥65 years with a LLI and LLE up to 2 years in at least 2/3 of them, prescribed with at least 1 preventive medication, but following any kind of intervention targeted at deprescribing and measuring the outcomes of the intervention were included. Any dual-purpose medication, unless stated that it was for symptom relief, was considered to be preventive. Advanced state of LLI was considered to meet our inclusion criteria if the duration of LLE was not specified. Therefore, studies on those with LLI but considering patients at EOL, terminally ill, under palliative care or frail were included. Corresponding authors were approached if clarification on the LLI and LLE was necessary. We considered the intervention in any setting(s) including but not limited to home, pharmacy, clinics, nursing homes, residential long-term facilities, and hospitals.

Cross-sectional studies, case series and case-reports were excluded. Studies clearly stating exclusion of patients with terminal illness or under palliative care or EOL were excluded. Studies were excluded if they did not fall in the criteria of LLI and LLE, did not use a deprescribing guideline, did not determine outcomes after the intervention, and were undertaken in those with mean age <65 years. Conference proceedings, review articles, unpublished literature, ongoing studies and studies published in a language other than English were also excluded.

2.5 | Comparator(s)/control

The comparator of the intervention was usual care or any head-to-head intervention.

2.6 | Outcomes of intervention

- *Primary outcome:* Medication appropriateness defined by a reduction in PIM or PIP or unnecessary medicine and assessed by any implicit and explicit criteria.
- *Secondary outcomes:* Clinical outcomes included mortality, QOL, falls, sleep quality, bowel function, cognitive function, performance status and symptoms status. The outcomes associated with cost included overall cost, medication cost and health care expenditure.

2.7 | Search strategy

The literature search was conducted in the databases PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Google Scholar. Keywords and controlled vocabulary were used with appropriate Boolean logics, synonyms and limiters. We included all original articles that were in English language from inception of the database to February 2019. The detailed search strategy is presented in Appendix 1. The reference lists of included studies and relevant reviews were manually explored for eligibility.

2.8 | Data extraction

- *Screening and study selection:* S.S. and A.P. independently performed the initial screening of title and abstract. Also, the full text of the selected articles was assessed by S.S. and A.P. Any disagreements were resolved with a consensus involving additional assessment by K.S. and L.N.
- *Data extraction and management:* A preagreed data extraction template was developed that included information on study design, demographics and baseline characteristics of study participants, settings, geography, sample size, medication appropriateness assessment tools, deprescribing intervention(s), and outcomes of intervention(s). Corresponding authors were approached for missing or ambiguous information, where necessary.

2.9 | Risk of bias (quality) assessment

S.S. initially assessed the risk of bias of each study and A.P. confirmed them, with verification by K.S. and L.N. Cochrane risk of bias tool, Risk Of Bias In Non-randomised Studies–of Interventions (ROBINS-I) tool, National Institute of Health's Quality Assessment Tool for Before–After Studies with No Control group tool and Newcastle–Ottawa Scale were used for the assessment of RCTs, quasi-experimental non-randomised controlled studies, pre-experiment pre–post studies and observational pre–post studies, respectively.

2.10 | Strategy for data synthesis

The studies included in our review showed heterogeneity in study design, outcomes, analyses and reporting. Therefore, meta-analysis was not performed. Data was presented on the basis of the characteristics of participants (age, gender/sex, type of LLI), settings, deprescribing intervention, intervention providers, medication inappropriateness, follow-up periods and outcome measures.

3 | RESULTS

3.1 | Results of search

A total of 9767 records were identified through electronic databases. After the removal of 1655 duplicates, 8112 titles and abstracts were

TABLE 1 Characteristics of included studies (n = 9) of the systematic review arranged according to study design

Author, y, country, setting	Study design, follow up	Participants	Inclusion criteria	Deprescribing intervention	Comparison	Outcomes
Frankenthal *et al.*,[27] 2017, Israel, RACF	RCT, at 12 and 24 mo	306 residents (I: 160; C: 146), age ≥65 y, 67.3% female, LLI (53.6% dementia, 23.2% IHD, 9.8% CHF), frail	Age ≥65 y, prescribed at least 1 daily medicine	Medication review by pharmacist using STOPP/START criteria followed by decision of chief physician	I (n = 126) and C (n = 126)	• *PIP (STOPP criteria)*: Baseline (I: 69.0% *vs* C: 61.9%); 12 mo (I: 23.0% *vs* C: 52.4%); 24 mo (I: 33.3% *vs* C: 48.4%, P = .002) • *Medications*: Baseline (I: 8.7 ± 3.3 *vs* C: 8.1 ± 3.0); 12 mo (I: 7.2 ± 2.6 *vs* C: 8.9 ± 3.2); 24 mo (I: 7.2 ± 2.8 *vs* C: 8.2 ± 3.2, P = .03) • *Costs*: I *vs* C at 24 mo (P < .001) • *Falls*: Baseline (I: 1.37 ± 2.5 *vs* C: 1.4 ± 2.6); 12 mo (I: 0.8 ± 1.4 *vs* C: 1.3 ± 2.5); 24 mo (I: 0.9 ± 1.4 *vs* C: 0.7 ± 1.4, P = .400)
Potter *et al.*,[28] 2016, Australia, RACF	RCT, at 6 and 12 mo	95 residents, age 84.3 y, 52% female, LLI (>75% dementia, 16% cancer), frail	Age ≥65 y, taking regular medicines	An individualised comprehensive medication review followed by stopping nonbeneficial medications conducted by a general practitioner and a geriatrician/clinical pharmacologist	I (n = 47) and C (n = 48)	• *Medications per participant:* Baseline (I: 9.6 ± 5.0 *vs* C: 9.5 ± 3.6); 6 mo (I: 7.3 ± 3.1 *vs* C: 9.7 ± 2.5, P < .001); 12 mo (I: 7.7 ± 4.1 *vs* C: 9.6 ± 3.5, P = .04) • *Mortality:* I: 26.0% *vs* C: 40.0% control, P = .16, HR 0.60, 95% CI 0.30–1.22 • *QOL score (QOLAD):* Baseline (I: 33 ± 6 *vs* C: 32 ± 6); 6 mo [I: [a]32.3 ± 4.4 (n = 23) *vs* C: [a] 31.8 ± 4.8 (n = 22)]; 12 mo [I: [a]32.0 ± 4.3 (n = 22) *vs* C: [a]31.0 ± 4.7 (n = 15); P = .94 • *One or more falls:* I: 0.56 (95% CI 0.42–0.69) *vs* C: 0.65 (95% CI 0.50–0.77), P = .40
Kutner *et al.*,[29] 2015, US, Inpatients	RCT (unblinded, parallel); up to 12 mo	381 patients, age 74.1 y, 44.9% female, LLI (48.8% cancer, 58.0% CVD)	Age ≥18 y, receiving statin for ≥3 mo, advanced LLI with life expectancy 1–12 mo, recent decline in functional status	Discontinuation of statin on the basis of randomisation in coordination of clinical research coordinator with physician or primary care provider	I (n = 189) and C (n = 192)	• *Mortality (60 days):* I: 23.8% *vs* C: 20.3% (90% CI -3.5 to 10.5%, P = .36) • *Survival (median time to death):* I: 229 d (90% CI 186 to 332 d) *vs* C: 190 d (90% CI 170 to 257 d), P = .60

(Continues)

TABLE 1 (Continued)

Author, y, country, setting	Study design, follow up	Participants	Inclusion criteria	Deprescribing intervention	Comparison	Outcomes
						• *Cardiovascular related events:* I: 54.2% *vs* C: 45.8% • *QOL score (McGill QOL):* I: 7.11 *vs* C: 6.85 (~AUC difference 0.26, 95% CI 0.02 to 0.50, *P* = .04) • *Symptom score (Edmonton Symptom Assessment System):* I: 25.2 *vs* C: 27.4, *P* = .13 • *Statin specific score:* I: 7.0 *vs* C: 7.2, *P* = .71 • *Performance score (Australian-Modified Karnofsky Performance Status):* I: 47.7 *vs* C: 48.5, *P* = .63 • *Cost saving due to statin discontinuation:* $3.37/d, 95% CI 2.83–3.9
Garfinkel *et al.*,[30] 2007, Israel, Inpatients	Quasi-experimental; at 12 mo	190 patients, age 81.6 y, 31.0% male, LLI (93.5% dementia), frail	Frail elderly	Geriatric–palliative approach algorithm led by physician	I (*n* = 119) and usual care (*n* = 71)	• *Mortality (1 y):* I: 21.0% *vs* C: 45.0%, *P* < .001 • *Referral to acute care facilities (1 y):* I: 11.8% *vs* C: 30.0%, *P* < .002
Whitman *et al.*,[31] 2018, US, Inpatients	Pre-experimental one group pre–post; before and after	26 patients, age 81 y, 54.0% male, LLI (all cancer), [b]LLE 1–2 y in >50%	Age ≥65 y with cancer	Comprehensive medication review by interdisciplinary team led by pharmacist	Pre- and postintervention (*n* = 26)	• *PIMs (Beers, STOPP, MAI):* 73% (*n* = 119) PIM deprescribed • *Medication per patient:* Preintervention: 12.0 ± 6.8 *vs* postintervention: 9.0 ± 3.0 postintervention • *Health care expenditure per person:* US$4282.27 potentially avoided • *Drug interaction:* 94 clinically relevant identified, 9 relevant with anticancer therapies identified • *Postintervention effect:* 16 patients had reduction of symptoms and side effects

(Continues)

TABLE 1 (Continued)

Author, y, country, setting	Study design, follow up	Participants	Inclusion criteria	Deprescribing intervention	Comparison	Outcomes
Poudel *et al*.,[32] 2015, Australia, RACF	Observational pre–post (single cohort); before and after	153 residents, age 83.0 y, 64.1% female, LLI (67.3% dementia), frail	Frail older people with regular access to geriatric consultations via video conferencing	Comprehensive geriatric assessment by senior registered nurse followed by video conferencing by geriatricians	Pre- and postintervention (*n* = 153)	• [c]HRM 2.6% dose altered, 17.2% dose stopped and 2.6% new drug started • *Medication per patient:* Preintervention: 9.6 ± 4.2 *vs* postintervention: [a]9.3 (out of total 1469 medicines; 145 stopped, 51 adjusted for dose and 101 new started)
Molist Brunet *et al*.,[33] 2014, Spain, Inpatients	Observational pre–post (single cohort); from admission to discharge	73 patients, age 86.1 y, 79.5% female, LLI (all dementia)	Advanced dementia	Comprehensive medication review in 3 stages by 2 geriatricians and a clinical pharmacist	Admission and discharge (*n* = 73)	• *Medication per person:* Admission: 7.3 *vs* discharge: 4.8, $P < .05$
Saad *et al*.,[34] 2012, US, Inpatients	Observational pre–post; from admission to discharge	62 patients, age 84.6 y, 79% male, LLI (53.0% dementia, 21.0% cancer), frail	Frail elder requiring geriatric consultation	Chart review by geriatric consultants	Admission and discharge (*n* = 62)	• *Medication per patient*: Admission: 7.7 ± 3.7 *vs* discharge: 9.5 ± 3.6 • *Cost*: Average increase of US$102 (range −343 to 2607)
Suhrie *et al*.,[35] 2009, US, Inpatients	Observational pre–post (single cohort); from admission to close-out	89 patients, age 76.7 y, 97.8% male, LLI (39.3% dementia, 16.9% cancer, 11.2% CVD), near the end-of-life	Older veterans who died in geriatric palliative care unit	Interdisciplinary geriatric palliative care team staffed by specialists	Admission and last 30 d of chart review just before death (*n* = 89)	• *Unnecessary medication (MAI):* Admission: 1.7 ± 1.5 (74.2%) *vs* close-out: 0.6 ± 0.8 (39.3%), $P < .001$ • [a]*Medication:* Admission: 9.7 *vs* discharge: 8.9

[a]Calculated from the data in the study;
[b]Information provided by author;
[c]Assessed through a list of high-risk medications (HRM) based on Beers Criteria 2012, McLeod Criteria, Laroche criteria, PRISCUS criteria and Norwegian General Practice criteria.
Age: mean age; AUC: area under curve; C: control group; CVD: cardiovascular disease; CHF: congestive heart failure; DVA: Department of Veterans' Affairs; HR: hazard ratio; I: intervention group; IHD: ischaemic heart disease; LLI: life limiting illness; LLE: limited life expectancy; MAI: Medication Appropriateness Index; QOL: quality of life; QOLAD: Quality of Life in Alzheimer's Dementia; RACF: residential aged care facility/facilities; PBS and RBS: The Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes; RCT: randomised controlled trial; STOPP: Screening Tool of Older People's Prescription; START: Screening Tool to Alert to Right Treatment

screened, and 122 of them were assessed for eligibility through full-text articles. One study was included from manual search of reference lists in publications. Finally, 9 studies[27-35] meeting the eligibility criteria were included and their characteristics are summarised in Table 1. During the review process, 1 study[27] quoted its previous study[36] for the baseline data. Therefore, our study used the data from both of the studies considering them as a single study and thus, the citation only indicates the latest reference. Details on the selection of studies is summarised in Figure 1.

3.2 | Description of studies

A total of 9 studies were evaluated for deprescribing interventions and their outcome measurements in individuals with a mean age of

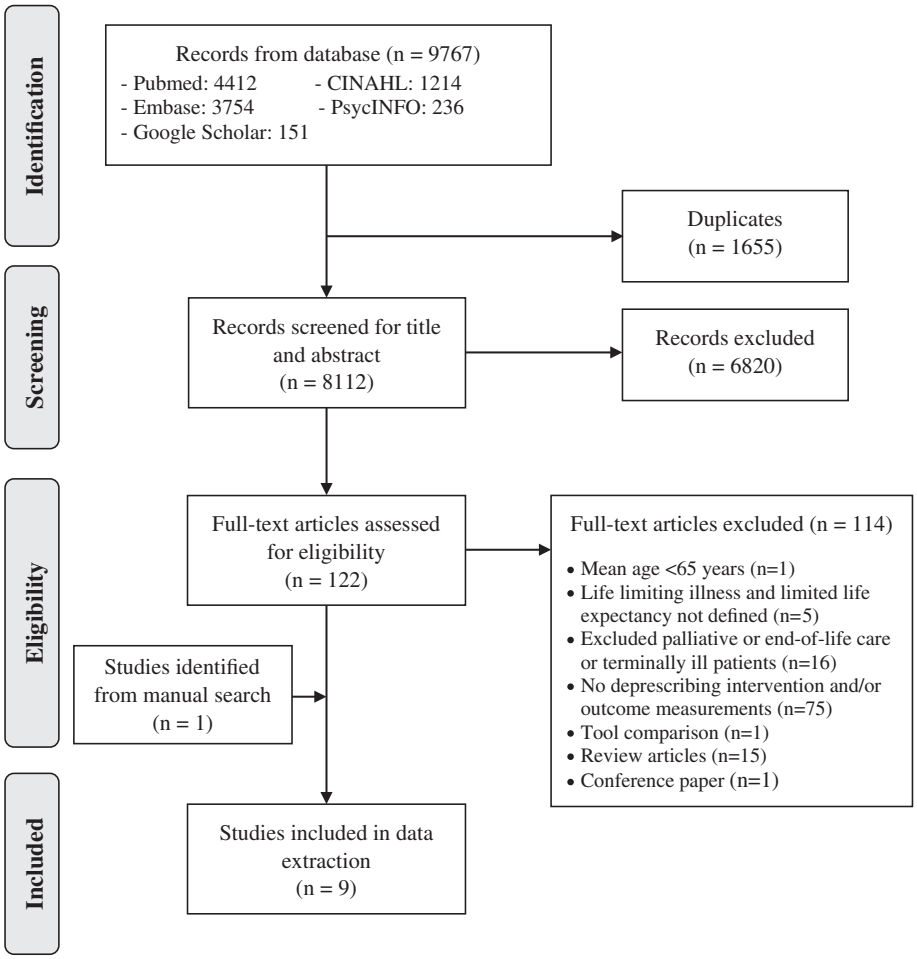

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of screening process

65 years and above, with at least 1 LLI present in >2/3 of each of their study population, and with evidence that they are at the EOL.

3.3 | Study characteristics

3.3.1 | Study design

There were 3 RCTs,[27-29] 1 quasi-experimental (controlled but not randomised) study,[30] 1 pre-experimental one-group pre–post study,[31] and 4 observational pre–post studies.[32-35]

3.3.2 | Country

Of the 9 studies, 4 of them were from the US,[29,31,34,35] 2 were from Australia,[28,32] 2 were from Israel[27,30] and 1 from Spain.[33]

3.3.3 | Participants and setting

Overall the included studies involved 1375 participants with mean age ranging from 74.1 years[29] to 86.1 years[33] and conducted in a hospital setting[29-31,33-35] (n = 821) or residential aged care facilities (RACF)[27,28,32] (n = 554). In 6 out of 9 studies,[27,28,30,32,33] more than half of the study population were female.

3.3.4 | Life-limiting illness

Six of the selected studies consisted of more than 1 LLI that included dementia (39.3–93.5%)[30,35] and cancer (16.0–48.8%)[28,29] as common illnesses but also cardiovascular diseases (CVDs), chronic obstructive pulmonary disease and others. One study each was carried out on the specific LLIs, cancer[31] (n = 26) and dementia[33] (n = 73).

3.3.5 | Deprescribing interventions

There were 5 studies that directly aimed at deprescribing medication.[28-31,35] In the remaining 4 studies,[27,32-34] the intervention was medication optimisation and not specifically direct deprescribing. However, withdrawal or reduction or discontinuation of medication was observed after an intervention, so these interventions indirectly led to deprescribing.

The 5 studies directly aiming to undertake a deprescribing intervention involved the following:

a. Individualised medication review followed by a planned cessation of nonbeneficial medicines by a general practitioner and a geriatrician/clinical pharmacologist.[28]
b. Discontinuation of a statin by physician or primary care provider.[29]
c. Use of geriatric–palliative approach algorithm to stop medication, led by a physician.[30]
d. Sequential medication review using 3 PIM identification tools (Beers criteria, Screening Tool of Older People's Prescription [STOPP] criteria and MAI) followed by multidisciplinary team-patient discussion for deprescribing.[31]
e. Interdisciplinary geriatric palliative care team assessing unnecessary medication use through MAI.[35]

The 4 studies that deprescribed medication as a part of overall medication optimisation included medication review by a multidisciplinary team as follows:

a. Review by a pharmacist using STOPP/START (START: Screening Tool to Alert to Right Treatment) criteria followed by decision of chief physician.[27]
b. Comprehensive geriatric assessment by senior registered nurse followed by video conferencing by geriatricians.[32]
c. Comprehensive medication review in a 3-stage process starting initially from patient centred assessment to diagnosis centred assessment and then finally medication centred assessment (if applicable also evaluated by STOPP/START or Beers criteria) by 2 geriatricians and a clinical pharmacist.[33]
d. Chart review by geriatric consultants.[34]

3.4 | Outcome measurement

3.4.1 | Primary outcome

The primary outcome of our study was medication appropriateness—reduction in PIMs or reduction in PIPs or reduction in unnecessary medications. Of the studies included, 4 studies assessed medication appropriateness. One study used the STOPP criteria to determine PIP[27]; the second study assessed PIM sequentially, starting from Beers criteria first, then the STOPP criteria, followed by MAI[31]; the third study assessed high-risk medications using Beers criteria, McLeod criteria, Laroche criteria, PRISCUS criteria and Norwegian General Practice criteria[32]; while the fourth used MAI.[35]

3.4.2 | Secondary outcomes

We have broadly classified the secondary outcomes into 3 groups because of the heterogeneity of the outcome measurements. Each of them are briefly discussed below:

a. *Medication-related outcomes:* Medication-related outcomes such as the number of medications, polypharmacy and drug interaction were identified. Number of medication and/or polypharmacy was measured by 7 studies.[27,28,31-35] One study determined drug interaction linked with anticancer therapies.[31]
b. *Clinical outcomes:* Two RCTs[28,29] and a quasi-experimental study[30] compared mortality between the intervention and control groups. One of the RCTs[29] also determined median survival time, proportion of unplanned hospitalisations, and performance status measured using Australian–Modified Karnofsky Performance status score. Both RCTs measured QOL; the trial in which dementia was prevalent used self-reported QOL using Quality of Life in Alzheimer's Dementia (QOLAD)[28] and the study in which cancer was predominant used the McGill QOL Questionnaire.[29] The third study assessed annual referral rate to acute care facilities.[30] Comprehensive measurements on several clinical aspects such as sleep quality, bowel function, cognitive function, physical function and self-reported health status were made by 1 of the RCTs.[28] This study also measured sleep quality using Neuropsychiatric Index–Nursing Home Version, bowel function using a bowel chart, cognitive function using a Mini Mental Status Examination, physical function as a proxy with the Modified Barthel Index, and general health status.[28] One of the RCTs used the Edmonton symptoms assessment system and statin-specific symptom supplemented in Edmonton score[29] to determine symptom status.

The pre-experimental study, which had a pre–post design[31] measured the overall reduction of symptoms together with side effects without the aid of a scoring system. Similarly, 2 RCTs determined falls; 1 of them determined the number of participants experiencing a fall or nonvertebral fracture confirmed radiologically[28] and the other reported the average number of falls in intervention and control groups.[27]

c. *Cost-related outcomes:* Cost was compared by 4 of the studies, covering all study types.[27,29,31,34] One RCT determined cost saving attributable to statin therapy discontinuation[29] and another RCT determined overall costs.[27] Similarly, a pre-experimental pre–post design determined health care expenditure[31] and an observational pre–post study compared cost at admission and discharge.[34]

3.5 | Risk of bias

As different methodological approaches were used by each of the included studies, the risk of bias was assessed using a variety of tools. The risk of bias of 3 RCTs[27-29] was assessed by the Cochrane risk of bias tool (Table 2). In general, the studies had low risk of most kinds of bias. However, in 1 study blinding was not clear.[27] For 2 others, either the risk due to failure of allocation concealment[28] or blinding of participants and personnel[29] was present. These 2 studies were also judged to be at high risk of other bias due to small sample size[28] and changes in the primary end points to the proportion of deaths within 60 days of trial enrolment.[29]

The risk of bias in the quasi-experimental non-randomised controlled study[30] was assessed as having a serious risk of bias (Table 3), while the risk of the pre-experimental study with pre–post design,[31]

TABLE 2 Risk of bias assessments for the randomised controlled trials in this review

Types of bias	Author, y		
	Frankenthal *et al.*, 2017[27]	Potter *et al.*, 2016[28]	Kutner *et al.*, 2015[29]
Random sequence generation	+	+	+
Allocation concealment	+	–	+
Blinding of participants and personnel	?	+	–
Blinding of subjective outcome assessments	?	+	+
Blinding of objective outcome assessment	+	+	+
Incomplete primary outcome data	+	+	+
Incomplete secondary outcome data	+	+	+
Selective reporting	+	+	+
Other bias	+	–	–

+, low risk; –, high risk; ?, unclear.

which had no control, had an overall score of *moderate* risk of bias (Table 4). There were 4 observational pre–post studies[32-35] and their risk of bias was assessed using the Newcastle–Ottawa scale (Table 5). All the studies showed 2 stars in the selection domain, with non-applicability in 2 questions of this domain, and 3 stars in the outcome domain. The comparability domain was not applicable as these were single cohort studies. Hence, the quality of the study (exclusive of nonapplicability) was relatively good based on the overall score (5 stars).

3.6 | Intervention effects

The effects of interventions are presented in Table 1.

3.7 | Primary outcome

The effect of an intervention in this review was primarily measured in terms of medication appropriateness. One RCT,[27] 1 pre-experimental pre–post study[31] and 2 observational pre–post studies[32,35] determined medication appropriateness. The RCT used STOPP criteria to measure PIPs and found a significant reduction of such prescriptions by 35.7% at 24 months ($P < .001$) after a deprescribing intervention compared to 13.5% reduction in control group ($P = .003$). Similarly, in the same study, a 4.8% reduction of potential prescription omission was also apparent in intervention group ($P = .43$) compared to 6.3% rise in the control group ($P = .24$) at 24 months.[27] The pre-experimental pre–post study reported that 73% ($n = 119$) of PIMs were deprescribed using the 3 assessment tools (Beers, STOPP and MAI).[31] One of the observational pre–post studies found that a significant reduction of 34.9% unnecessary medication use as measured by MAI occurred after an intervention from admission to close-out ($P < .001$).[35] The other observational pre–post study reported that for high-risk medicines the intervention stopped 17.2% and altered the dose of 2.6%; however, a significant difference was not measured.[32]

3.8 | Secondary outcomes

3.8.1 | Medication-related outcomes

a. *Number of medications and/or polypharmacy:* Change in the number of medications and/or polypharmacy was reported by 7 studies[27,28,31-35] (Figure 2). Two of these studies were RCTs[27,28] that reported a significant ($P < .05$) reduction in mean number of medications between intervention group (from 8.8 ± 3.4, $n = 183$ to 7.3 ± 2.7, $n = 160$ and from 9.6 ± 5.0 to 7.7 ± 4.1, $n = 47$) and control group (from 8.2 ± 3.0, $n = 176$ to 8.9 ± 3.2, $n = 146$ and from 9.5 ± 3.6 to 9.6 ± 3.5, $n = 48$) over a 12 months period. One observational pre–post study[33] reported a significant reduction of medications from 7.3 on pre-intervention (admission) to 4.8 on post-intervention (discharge). The other 4 studies[31,32,34,35] reported a decrease (12.0 to 9.0; 9.6 to 9.3; 9.7 to 8.9, respectively) or increase (7.7 ± 3.7 to 9.5 ± 3.6) in number of medication before and after intervention but statistical analysis was not provided.

b. *Drug interaction:* The pre-experimental pre–post study showed that all 16 patients who had reported symptoms and side effects attributable to polypharmacy and PIMs had reduction in symptoms and side effects after intervention.[31]

3.8.2 | Clinical outcomes

a. *Mortality:* Two RCTs[28,29] and the quasi-experimental study[30] reported on mortality and/or survival. The RCTs reported changes in the overall mortality percentage but no significant difference in the mortality between intervention group and control group at 60 days (23.8% intervention *vs* 20.3% control, $P = .360$)[29] and 12 months follow-up period (26.0% intervention *vs* 40.0% control, $P = .160$).[28] The quasi-experimental study reported a significant decrease in mortality at 12 months (21.0% intervention *vs* 45.0% control, $P = .001$)[30] as shown in Figure 3.

b. *Quality of life:* The QOL was measured by 2 RCTs, in which 1 of them had predominantly dementia[28] while the other had cancer.[29] The former study showed no significant difference in the QOL between those with and without intervention even after adjustment for age, sex and number of regular medication at baseline.[28] However, the other study showed higher QOL value among those whose statin was discontinued as compared to control (7.1 *vs* 6.9) and this difference was significant at $P = .04$ (95% confidence interval 0.02–0.50).[29]

c. *Falls:* There were 2 RCTs[27,28] that reported the effect of intervention on number of falls. One study reported significant reduction

TABLE 3 Risk of bias assessment of quasi-experimental nonrandomised controlled study using the ROBINS-I tool

Author, y	Confounding	Selection	Classification	Deviation from intervention	Missing data	Measurement of outcomes	Selection of outcomes	Overall
Garfinkel *et al*., 2007[30]	Serious	Serious	Low	Low	Low	Low	Low	Serious

TABLE 4 Quality assessment of the pre-experimental study using National Institute of Health's quality assessment tool for before–after (pre–post) studies with no control group

Criteria	Author, year (Whitman *et al*., 2018)[31]
Was the study question or objective clearly stated?	Yes
Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes
Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes
Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
Was the sample size sufficiently large to provide confidence in the findings?	CD
Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes
Were the outcome measures prespecified, clearly defined, valid, reliable and assessed consistently across all study participants?	Yes
Were the people assessing the outcomes blinded to the participants' exposures/interventions?	CD
Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No
Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *P* values for the pre-to-post changes?	No
Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No
If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level? *if this question is not applicable, total score is out of 11, not 12.	NA
Add scores for each criterion together and divide by 12. Risk of bias rating: low (75–100%), moderate (25–75%), or high (0–25%)* OVERALL SCORE: 6/11	Moderate

CD: Cannot determine, NA: not applicable

in the number of falls at 12 months in the intervention group (from 1.3 ± 2.4 to 0.8 ± 1.3, P = .006, n = 160) but not in the control group (from 1.4 ± 2.5 to 1.3 ± 2.4, P = .66, n = 146).[27] The average falls and its prevalence was not significantly different among the groups at this time (P = .28) and from 12 to 24 months (P = .40). However, there was significant reduction in the average number of falls when compared between baseline to 24 months in both the intervention (from 1.4 ± 2.5 to 0.9 ± 1.4, P = .04, n = 126) and control (from 1.4 ± 2.6 to 0.7 ± 1.4, P = .008, n = 126) groups.[27] In another study the proportion of falls between intervention and control group was not significantly different (0.6 *vs* 0.7, P = .40) during the trial period of 12 months.[28]

d. *Other clinical outcomes:* One RCT reported no significant difference in the sleep quality, bowel function, cognitive function, physical function and general health status between intervention and control groups.[28] The other RCT reported no significant difference between intervention and control groups at 12 months in terms of the performance status (47.7 *vs* 48.5, P = .63) and symptom status (25.2 *vs* 27.4, P = .71).[29]

3.8.3 | Cost-related outcomes

a. *Overall cost:* One RCT reported a significant difference (P < .001) in the cost between intervention group and control group at 12 months and 24 months.[27] An observational pre–post study depicted an increase in a cost of US$102 (ranging from −343 to 2607) from admission to discharge.[34]

b. *Medication cost:* One RCT reported a cost saving of US$3.37 per day (95% confidence interval 2.83–3.91) after discontinuation of statin therapy.[29]

c. *Health care expenditure:* A pre-experimental pre–post study in the USA suggested a potential reduction of US$4282.27 per person on health care expenditure after intervention.[31]

4 | DISCUSSION

We identified 9 studies through this systematic review, 3 randomised and 6 non-randomised studies, evaluating the outcomes of deprescribing intervention in older patients with LLIs and LLE. Studies

TABLE 5 Quality assessment of observational pre–post studies using the Newcastle–Ottawa scale

Criteria		Author, y			
		Poudel *et al.*, 2015[32]	Molist Brunet *et al.*, 2014[33]	Saad *et al.*, 2012[34]	Suhrie *et al.*, 2009[35]
Selection (maximum 4 stars)	Representativeness of the exposed cohort	★	★	★	★
	Selection of the nonexposed cohort	NA	NA	NA	NA
	Ascertainment of exposure	★	★	★	★
	Demonstration that outcome of interest was not present at the start of the study	NA	NA	NA	NA
Comparability (maximum 2 stars)	Comparability of cohort on the basis of the design or analysis	NA	NA	NA	NA
Outcome (maximum 3 stars)	Assessment of outcome	★	★	★	★
	Was follow-up long enough for outcomes to occur	★	★	★	★
	Adequacy of follow-up of cohorts	★	★	★	★
Overall quality	Total number of stars (0–9)	5	5	5	5

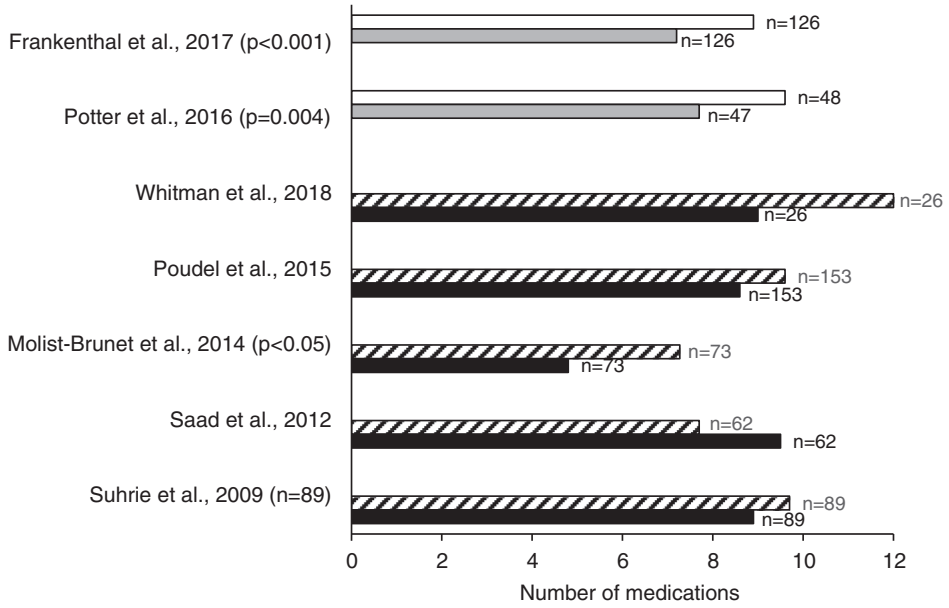

FIGURE 2 The effect of deprescribing intervention on the number of medications for 2 randomised controlled trials[27,28] showing intervention (grey bars) compared to the control (white bars) in 12 months and 5 observation pre–post study[31-35] showing the pre-intervention (patterned bars) compared to the post-intervention (black bars)

were conducted in hospitals and RACFs, and the majority of the participants were female. Each study approached deprescribing differently but our review showed that deprescribing intervention could improve medication appropriateness in older people with LLI (commonly cancer and dementia) and LLE. Additionally, the findings for clinical outcomes revealed that, while there is generally a decline in mortality after intervention, this was not always statistically significant, and there were inconsistent outcomes in QOL and number of falls. Several other clinical outcomes such as sleep quality, bowel function, cognitive function, physical function, general health, performance and symptoms were also reported but changes in the intervention group were not significantly different to that of the control group. We explored the cost-related outcome and although the potential for cost savings was not assessed in all studies there was an indication of cost savings resulting from deprescribing.

4.1 | Outcomes

Exposure to PIMs among older people living in nursing homes is high, and therefore effective interventions for medication optimisation are essential to minimise prevalence.[37] PIM use has been known to be associated with adverse drug reactions.[38] One study in our review stated that a deprescribing intervention reduced the symptoms and side effects related to polypharmacy and PIMs.[31] Also 2 studies[27,35] reported a significant reduction in medication inappropriateness after intervention. Another study showed intervention ceased around 1/5

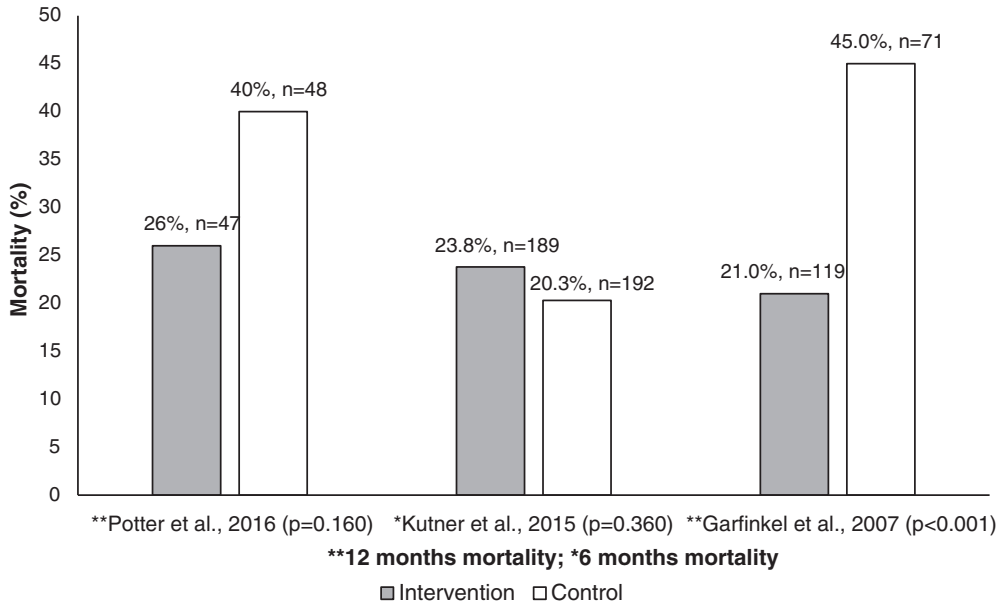

FIGURE 3 The effect of deprescribing intervention on mortality for 2 randomised controlled trails[28,29] and 1 quasi-experimental study[30] showing the intervention (grey bars) compared to the control (white bars)

of high-risk medications.[32] Previous reviews have shown that deprescribing interventions minimise PIM use in RACFs[39] and hospitals.[40]

Our review showed a reduction in the number of medicines after deprescribing intervention in 6 studies[27,28,31-33,35] but the statistical significance remains to be established. Use of high number of medications may increase the risk of several medicine-related harms[41-44] potentially due to risk of more inappropriate medication use.[45-49] It is evident from our study that despite the variation in deprescribing intervention, a reduction in the number of medicines was observed in almost all studies. A meta-analysis of studies involving older individuals recommends testing interventions in pragmatic RCTs because there is insufficient evidence that interventions reduce numbers of inappropriate medications, and to determine impact on clinical outcomes.[50] Although the meta-analysis was not specific to LLI or in those with LLE, the recommendation is also likely to be relevant to this population in terms of improving clinical measures during the EOL.

The findings of this review suggest an overall reduction in the percentage of mortality, in both RACFs and hospitals. The reduction was either significant compared to control group or no different to the control group, as assessed at 6 or 12 months after intervention. Evidence in the literature regarding reduction in mortality as a result of deprescribing is conflicting. A systematic review by Kua *et al.*[39] using subgroup analysis found medication review-directed deprescribing intervention reduced all-cause mortality, but another systematic review and meta-analysis[51] reported no reduction in mortality and hospitalisation in nursing home residents after a medication review intervention. However, there was no clear indication that either of these reviews included studies undertaken solely on patients with LLI or under palliative care. More importantly, our review suggests that deprescribing may not accelerate death in patients under palliative care.

The measure that is as a high priority by older patients with terminal illness, their caregivers and health care professionals is QOL.[52,53] In our study QOL was reported by 2 RCTs and the effect of deprescribing on QOL was found to be inconsistent. The discrepancy might be due to the variation in QOL measurement tool and the difference in the predominant LLI in the studies. One study was higher in percentage of participants with dementia and used the QOLAD tool, finding that QOL reduced. The other had a higher proportion of cancer patients and used the McGrill QOL questionnaire, finding that QOL improved. As there is significant variation in trajectory of LLIs,[54] this must be considered when taking into account the impact of deprescribing intervention on clinical outcomes, including mortality and QOL.

We found no clear evidence that deprescribing intervention reduces the number of falls. Several reasons might have influenced the outcomes. Two RCTs[27,28] that reported on falls had variation in sample size, LLI and intervention. Also, both studies were conducted in RACFs. However, a systematic review in participants other than those at the EOL shows a 24% reduction in the number of falls after a deprescribing intervention. This reduction was responsible for an estimated cost saving of US$1049–3611 per injury to the health care system.[39] One of the RCTs included in our review, which found a significant reduction in the number of falls, also found the same kind of reduction in the overall cost but the saving was not attributed to falls.[27] In contrast, another study[34] in our review reported an increase in cost after their intervention, in which the average number of medications also increased, although the cause of the rise in cost could not be specifically attributed to number of medication or any other reason. Overall our review depicts a potential cost saving after an intervention.

A number of other clinical outcomes were explored by 2 studies.[28,29] One study reported on sleep quality, bowel function, cognitive function, physical function and general health status.[28] The change in these qualities after the intervention was not significant but an improvement in sleep quality and bowel function was observed. Although this RCT involved direct deprescribing and blinding of researcher assessing subjective measurements, there were some

major drawbacks such as small sample size, lack of concealment of allocation and reliability of reporting of some outcomes due to a higher number of participants with dementia. In another RCT that focused on discontinuation of statins, no improvement in performance status (activities of daily living) and symptoms was reported.[29]

4.2 | Deprescribing

The studies included in our review used several tools during the deprescribing process such as STOPP/START, STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy), Beers criteria, MAI, McLeod Criteria, Laroche criteria, PRISCUS criteria, Norwegian General Practice criteria or a combination of 2 or more tools. More recently a systematic review has identified 15 tools for deprescribing in frail older people with LLE.[55] These include models or frameworks for approaching deprescribing, tools for approaching deprescribing of the entire medication list, and tools for deprescribing of individual medications. Most of these tools have not yet been tested in clinical practice and their reliability in the clinical setting is not established. However, tools used in deprescribing interventions among those with LLE should also consider specific LLIs, since the disease trajectories vary significantly[54] and age-related pharmacokinetic and pharmacodynamic changes[22] also exist. The systematic review on tools for deprescribing[55] included some of those that are relevant for dementia.[56,57] A deprescribing guideline for cancer patients under palliative care, OncPal deprescribing guideline,[58] was not included in that review. This tool is validated but the clinical outcome or impact has to be established, consequently it was not included in the present review.

4.3 | Recommendations

This systematic review reveals that rigorous studies aiming to understand clinical outcomes of deprescribing interventions in patients with specific LLIs and with LLE is lacking. It is essential for studies to take into account the expected illness trajectories because of their variable nature. For example, typically, in cancer there is a steady progression and usually a clear terminal phase, while in people with dementia or frail older people, the progression is often a prolonged gradual decline.[54] Additionally, each study included in this review varied in intervention. This demands a clinically useful plan to cease medications before the EOL in specific LLIs, particularly addressing the challenge of deprescribing medications that have dual use (both preventive and symptom control) in high risk patients. Nonetheless, the validity of tools or guidelines used for deprescribing is crucial in the process. Therefore, with all the achievements so far, it is now appropriate to consider patient characteristics such as age, their disease patterns and settings during deprescribing.

4.4 | Strengths and limitations

There are certain limitations to our study. The interventions varied considerably in the approach to deprescribing, use of tools to identify PIMs and involvement of health care professionals. For example, 2 studies performed medication review but 1 followed a 3-stage process and used different tools in each stage, while the other only followed a review by geriatric consultants. Additionally, our study did not take into account the subjective nature of PIM measurement such as patient preferences, particularly with the use of implicit criteria, but the association of PIM with poor health outcomes cannot be neglected. Literature published in languages other than English were excluded, which may have led to language bias. Overall, the studies included in our review showed heterogeneity in study design, outcomes, analyses and reporting. Therefore, we did not perform a meta-analysis. Despite these limitations, to the best of our knowledge, this is the first study to specifically investigate the outcome of deprescribing interventions, particularly clinical measures, in older patients with LLI and LLE.

5 | CONCLUSION

Our study suggests that deprescribing interventions can improve medication appropriateness in older people with LLI and LLE. Although the interventions varied and were nonspecific to LLIs, deprescribing had potential for mortality reduction and cost savings but its impact on QOL and falls was not clear. More evidence is needed around the clinical impact of deprescribing in LLIs and LLE, and the effect on several other domains including physical, cognitive and psychosocial functioning could also be useful.

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COMPETING INTERESTS

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CONTRIBUTORS

S.S. conceived the work. S.S. and A.P. designed the study, and performed the screening. All authors decided on the final study selection and their quality assessment. S.S. performed the data extraction, data analysis and wrote the initial draft. All authors participated in writing and revising the manuscript, as well as read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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